REMARKS

Reconsideration and allowance are respectfully requested.

In this amendment, claims 1 and 15 are amended for further clarity. Support for the amendments can be found in the specification and claims as originally filed. For example, the specification at page 3, lines 19-20 discloses wild-type Factor VIIa. Factor VIIa having at least 110% of the bioavailability of a reference Factor VIIa is disclosed, e.g., at page 18, lines 11-12 and in Example 1. No new matter is added. Accordingly, claims 1-6, 8-15, and 17-24 are pending and claims 1-6 and 8-15 are at issue.

Priority

The Examiner has maintained that the present claims are entitled to a priority date of October 2, 2001, the filing date of US 09/969,357 (the "'357 application"). The Examiner contends that Danish priority application serial no. DK PA 2000 01456 (the "'01456 application"), filed October 2, 2000, discloses large-scale culture in medium lacking serum but not in medium lacking animal-derived components.

Applicants respectfully direct the Examiner's attention to page 12 of the Danish priority application, which states: "In a preferred embodiment, the growth medium that is added to the cells contains no protein or other component that was isolated from an animal tissue or an animal cell culture." On this basis, it is respectfully submitted that the present application is, in fact, entitled to a priority of October 2, 2000.

Information Disclosure Statement

Applicants again respectfully request clarification of the Examiner's initial indication that the Information Disclosure Statement filed December 2, 2003 was defective. As previously explained, a Form PTO-1449 was filed on the same date as the Information Disclosure Statement containing all of the references that the Examiner has labeled as being improperly disclosed. Furthermore, PAIR (entry of 8/9/06) indicates that the Examiner considered all of these references and initialed the PTO-1449 form. Applicants merely wish to eliminate any lack of clarity in the file that these references have not been considered.

Double Patenting

Claims 1-6, 8-11, and 15 have been rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-3, 5, 8, 10-13, and 15-17 of commonly assigned application serial no. 10/394,086.

It is believed that this response to the outstanding Office Action will remove all claim rejections other than this double patenting rejection. On that basis, it is respectfully requested that, should the claims be found to be in condition for allowance, the Examiner allow the claims to issue and maintain the double patenting rejections in the remaining application (M.P.E.P. 804).

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 10 has been rejected under 35 U.S.C. §112, second paragraph, for indefiniteness, based on a lack of antecedent basis for "the cell-containing carriers".

In this response, claim 9 has been amended to depend from claim 8, thus, it is believed, providing the requisite antecedent basis. It is believed that this amendment has overcome the rejection.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-6 and 8-15 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement and lack of written description. The Examiner contends that the term "Factor VIIa" encompasses variants of Factor VII that exhibit equal or improved biological activity and that the specification does not support the full scope of the claims nor indicate that Applicants had possession of the full scope of the claims at the time of filing.

While Applicants disagree with the Examiner's assertion, in order to expedite prosecution the claims have been amended herein to require that the Factor VII being produced by the claimed method is wild-type Factor VII. It is respectfully submitted on this basis that this rejection has been overcome.

Rejections Under 35 U.S.C. § 103

Claims 1, 2, 5, 6, 15, and 16 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Ragni, *Haemophilia* 7(supp 1):28-35, 2000; in view of Schmidtchen et al., *Am.J.Hum.Genet.* 62:64, 1998. The Examiner contends that Ragni discloses methods for large-scale production of Factor VII in recombinant cells in serum-containing cultures; that Schmidtchen et al.

disclose methods for protein production in recombinant CHO cells in the absence of serum; and that it would have been obvious to combine these teachings to achieve the presently claimed invention. This rejection is respectfully traversed.

As discussed above, Applicants believe that the present claims are entitled to the priority of DK PA 2000 01456 and that, consequently, Ragni is not prior art against the present claims (see above).

Furthermore, as discussed in the Amendment filed December 20, 2006, it is apparent from the scientific literature that, prior to the present invention, one of ordinary skill in the art could have had no reasonable expectation of success in practicing the present invention. As pointed out previously, Ragni suggests altering the sequence/structure of the clotting factors (see, e.g., page 32, first column- page 33, second column) as a way to overcome problems of immunogenicity and stability of recombinant proteins, not by optimizing production conditions as in the present invention.

Schmidtchen et al. is silent with regard to large-scale production in serum-free conditions and hence is not directly relevant to the present claims.

Applicants respectfully disagree with the Examiner that statements in the abstract of Ragni "provid[e] an expectation of success for the methods rendered obvious by the combination of Ragni et al. and Schmidtchen et al." (Final Office Action mailed March 9, 2007, at page 9.)

Ragni is a review article intended to summarize the state of the art in 2001. The article focuses on the well-known immunogenicity of Factor VIII and Factor IX (the first-line treatments for Hemophilia A and B, respectively) and contains general statements about the potential value of using protein-free methods to produce clotting factors recombinantly. Thus, the Ragni abstract states "……third-generation recombinant factor concentrates *currently in development* take advantage of new strategies to achieve a 'protein-free' cell culture, purification, and final formulation" (emphasis added.) Given the long lead times and uncertainty in clinical development (and the low probabilities of success in bringing pharmaceutical products to market), it is clear that the words "to achieve" represent a mere wish and not a statement of something already achieved. This cannot be the basis for a reasonable expectation of success that would be required to support a finding of obviousness. [1]

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1 Notably, the Ragni abstract also states: "Despite our best efforts……there continues to be a need to improve the margin of safety…" and "The hope is

Furthermore, the invention as currently claimed requires the Factor VIIa product to exhibit a higher availability than that of a reference preparation produced in the presence of serum. Ragni et al. is completely silent with respect to increased bioavailability.

For all of the above reasons, it is respectfully submitted that the present rejection is not well-taken and should be withdrawn.

Based on the above amendments and remarks, it is believed that the claims are in condition for allowance, and a determination to that effect is earnestly solicited.

Applicants believe that no additional fees are due. However, should any fees be due, the Commissioner is hereby authorized to charge any fees in connection with this application and to credit any overpayments to Deposit Account No. 14-1447.

Respectfully submitted,

Date: April 17, 2008

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that……treatment if hemophilia in the new millennium will be safer and less immunogenic", both of which highlight the uncertainties present at the time of Ragni.